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Deficits in visuo-spatial working memory, inhibition and oculomotor control in boys with ADHD and their non-affected brothers

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Summary. Few studies have assessed visuo-spatial working memory and inhibition in attention-deficit/hyperactivity disorder (ADHD) by recording saccades and consequently little additional knowledge has been gathered on oculomotor functioning in ADHD. Moreover, this is the first study to report the performance of non-affected siblings of children with ADHD, which may shed light on the familiality of deficits. A total of 14 boys with ADHD, 18 non-affected brothers, and 15 control boys aged 7–14 years, were administered a memory-guided saccade task with delays of three and seven seconds. Familial deficits were found in accuracy of visuo-spatial working memory, percentage of anticipatory saccades, and tendency to overshoot saccades relative to controls. These findings suggest memory-guided saccade deficits may relate to a familial predisposition for ADHD.

Keywords: ADHD; non-affected sibling; memory-guided saccade; endophenotype; overshoot; eye movement

Introduction

Patients with attention-deficit/hyperactivity disorder (ADHD) (American Psychiatric Association 1994) are known to have problems in working memory (Martinussen et al. 2005) and response inhibition (Oosterlaan et al. 1998). Structural and functional imaging studies have revealed that working memory is primarily controlled by the dorsolateral prefrontal cortex and basal ganglia (D'Esposito et al. 1995; Smith et al. 1998) and that patients with ADHD have an altered architecture and less activation of these areas compared to controls (Zametkin et al. 1990; Castellanos et al. 1996; Aman and Carmichael 1997; Rubia et al. 1999; Yeo et al. 2003; Dickstein et al. 2006). Inhibition is primarily mediated by the fronto-striatal circuitry and this circuitry has also been found to be involved in the pathology of ADHD (Durston et al. 2003; Schulz et al. 2004). Furthermore, the dopaminergic system plays an important role both in working memory and inhibition (Brozoski et al. 1979; Levy and Swanson 2001; Hazy et al. 2006) as well as in the pathology of ADHD (Levy 1991; Levy and Swanson 2001).

Infrequently documented is the use of eye movement (oculomotor) tracking systems to study visuo-spatial working memory and inhibition in ADHD. Oculomotor paradigms provide a means to examine dysfunctions at the interface between movement and cognition (Mostofsky et al. 2001). Such paradigms provide benefits over standard procedures to study working memory and inhibition (i.e., manual or computerized task without recording of saccades). First, the underlying brain mechanisms for the control of saccades are well documented (Schall 1991; Moschovakis 1996; Munoz 2002; Hall and Moschovakis 2003; Leigh and Kennard 2004). In turn, the knowledge on the underlying brain mechanisms of oculomotor control may shed light onto the underlying pathophysiology of ADHD, because affected oculomotor behaviour can pinpoint specific neurological problems (Leigh and Kennard 2004). Second, relative to reaction time data, saccades provide a much richer data set which allows a better understanding of the under-

An informed consent was obtained from all the participants and the rights of the participants were protected.

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lying mechanism (Cairney et al. 2001). Third, saccades recorded, while performing a task, may not only provide information regarding the process measured by the task, but also information regarding the metrics and dynamics of oculomotor control, such as the velocity, under-versus overshoot and duration of saccades.

A frequently used paradigm to assess visuo-spatial working memory by means of recording saccades is the memory-guided saccade task (Fuster 1990; Pierrot-Deseilligny et al. 1991; Brandt et al. 1998). Participants are instructed to look at a central fixation point. During this fixation, a target appears at a location in the peripheral visual field. The participant is not allowed to make a saccade towards the target but has to remember the location of the target. When the fixation point disappears, the participant is required to make a saccade towards the memorized location. The time between the disappearance of the target and the moment the participant is allowed to make a saccade (delay period) can be varied in order to vary the visuo-spatial working memory load. Longer delays hypothetically place heavier loads on (visuo-spatial) working memory than shorter delays (Sawaguchi and Goldman-Rakic 1994; Ozonoff and Strayer 2001). To perform a memory-guided saccade correctly, a participant must store and maintain an accurate internal representation of the target location in visuo-spatial working memory, because the saccade to the memorized position has to be executed in the absence of a visual stimulus.

The neurological substrates underlying performance on the memory-guided saccade task are well established: in addition to the brain areas active in basic oculomotor control (frontal eye field, parietal eye field, visual cortex, striatum, superior colliculus, cerebellum and brainstem loci) (Leigh and Zee 1999; Sweeney et al. 2004; Ettinger et al. 2005), memory-guided saccades activate the dorsolateral prefrontal cortex, anterior cingulate and supplementary eye field (Sweeney et al. 1996; Pierrot-Deseiligny et al. 2004; Ettinger et al. 2005). Memory-guided saccades are strongly mediated by dopaminergic neurotransmission since local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys cause impaired performance on memory-guided saccade paradigms (Brozoski et al. 1979; Sawaguchi et al. 1988; Sawaguchi and Goldman-Rakic 1994). Remaining fixated on the fixation cross while the target is presented in the peripheral visual field requires top-down control processes, mediated by the superior frontal, inferior parietal and superior temporal brain areas (Hopfinger et al. 2000). Since several of these brain areas and dopaminergic transmission have also been found altered in patients with ADHD (Zametkin et al. 1990; Castellanos et al. 1996; Aman and Carmichael 1997; Rubia et al. 1999; Durston et al. 2003; Yeo et al. 2003; Schulz et al. 2004; Dickstein et al. 2006), it is hypothesized that children with ADHD will have difficulty executing memory-guided saccades and remaining fixated during the fixation period.

However, research using memory-guided saccades in ADHD patients has revealed inconsistent results. Ross and colleagues (1994a, 2000) found no impairments in children and adults with ADHD in the accuracy and latency (reaction time) of saccades towards the memorized target. This contrasts with the results reported by Castellanos et al. (2000), who found girls with ADHD to be less accurate than control girls, but with comparable saccade latency. The opposite pattern was found by Mostofsky and colleagues (2001), who reported children with ADHD to be as accurate, though slower in their saccades to the memorized target. Only one of these studies examined whether a longer delay (three seconds) would emphasize group differences compared to a shorter delay (one second) by placing a heavier load on visuo-spatial working memory (Ross et al. 2000). This appeared not to be the case for adults with ADHD compared to normal adults. Findings thus far remain inconclusive, possibly due to differences between studies in delay periods used, ranging from 800 msec to 5000 msec.

The memory saccade task has also been used as an important indicator of response inhibition (Ross et al. 1994a, 2000; Castellanos et al. 2000; Mostofsky et al. 2001). Because participants have to suppress a potent response to the target, failures of response inhibition are expressed by anticipatory saccades to the target location. All cited studies above reported more anticipatory saccades in patients with ADHD (Ross et al. 1994a, 2000; Castellanos et al. 2000; Mostofsky et al. 2001). This consistent finding is also frequently reported in ADHD using paradigms other than the memory-guided saccade task, such as the antisaccade paradigm (Cairney et al. 2001; Klein et al. 2003; Feifel et al. 2004). Besides more frequent anticipatory saccades, there has also been reported an elevated number of intrusive saccades in ADHD patients (Gould et al. 2001; Klein et al. 2003; Munoz et al. 2003). Intrusive saccades are defined as inappropriate saccades during the fixation period and may also be regarded as tapping into response inhibition, since a significant correlation has been found between intrusive saccades and inhibition errors on an antisaccade paradigm (Munoz et al. 2003).

Memory saccade experiments may further be used to assess the metrics and dynamics of oculomotor control. Saccades towards the non-visual (memorized) target are less accurate, more variable at the endpoint, undershooting the actual location, and slower than saccades towards vi-

sual targets (Becker and Fuchs 1969; Henson 1979; Gnadt et al. 1991; White et al. 1994). These basic measures have not been thoroughly investigated in ADHD patients, although oculomotor measures such as under- versus overshoot, velocity and duration of saccades, can provide additional information concerning the neurological substrate of saccades. Munoz and colleagues (2003) reported a reduced peak velocity and an increased duration of saccades in children and adults with ADHD on a prosaccade task. However, Hanisch and colleagues did not replicate the findings for peak velocity and duration (Hanisch et al. 2006). It would seem worthwhile to further investigate the metrics and dynamics of oculomotor control in patients with ADHD.

In addition to studying memory-guided saccades in boys with ADHD, we also studied these saccades in their non-affected brothers. By including non-affected siblings, it might be possible to investigate whether or not deficits on the memory-saccade task relate to familial factors also causing ADHD (Durston et al. 2004). That is, non-affected siblings portray normal levels of in attention and hyperactivity/impulsivity. However, even though they are behaviourally normal, they still possess some of the causal genetic and environmental factors leading up to ADHD. In case non-affected siblings show (some) of the deficits also observed in their affected siblings, then it is feasible that the deficits are caused by a familial risk for ADHD and as such, form candidate endophenotypes: underlying vulnerability traits that heighten the risk for developing ADHD (Gottesman and Gould 2003; Waldman 2005). However, if deficits are only observed in affected children and not in their non-affected siblings, then it is less likely that the deficits relate to a familial risk for ADHD. In that case, the deficits may be caused by the presence of ADHD itself (i.e., being more inattentive, hyperactive, and impulsive causes a bad task performance) or relate to some unique risk factors for ADHD that are not shared between the affected and non-affected siblings. Either way, clarifying whether or not deficits are also present in non-affected siblings may shed light on direction of causality between memory-guided saccade deficits and ADHD.

This study aimed to investigate (1) whether boys with ADHD and their non-affected brothers show a decreased accuracy and latency in saccades towards the memorized target compared to controls, reflecting visuo-spatial working memory impairment, (2) whether boys with ADHD and their non-affected brothers show more anticipatory and intrusive saccades than controls, reflecting disinhibition and (3) whether boys with ADHD and their non-affected brothers could be dissociated from controls with respect to oculomotor control (i.e., velocity, under- versus overshoot, and duration of saccades). It was hypothesized that group differences would be larger when a seven-second delay was applied compared to a three-second delay, since a seven-second delay would hypothetically load more heavily on visuo-spatial working memory and inhibitory processes (Sawaguchi and Goldman-Rakic 1994; Ozonoff and Stayer 2001).

Materials and methods

Participants

Families with at least one child with the combined subtype of ADHD and at least one additional sibling (regardless of the presence of ADHD) were recruited in order to participate in the Amsterdam part of the International Multicenter ADHD Genes study (IMAGE). The IMAGE project is an international collaborative study that aims to identify genes that increase the risk for ADHD using QTL linkage and association strategies (Brookes et al. 2006). Additional control families were recruited from primary and high schools from the same geographical regions as the participating ADHD-families. Controls and their first degree relatives had no formal or suspected ADHD diagnosis.

For the current study, brothers aged between 7 and 14 years, who were discordant for ADHD were selected from the Amsterdam IMAGE-sample and asked to take part in an eye movement study consisting of an oculomotor capture task and a memory-guided saccade task (Van der Stigchel et al. 2007). Control boys aged between 7 and 14 years that had previously participated in the IMAGE-study, were asked to participate. Data for the memory-guided saccade task was available of 14 boys with combined subtype ADHD, 18 of their non-affected brothers and 15 control boys. All included boys were of European Caucasian descent and were excluded if they had an IQ < 70, a diagnosis of autism, epilepsy, general learning difficulties, brain disorders or known genetic disorders, such as Down syndrome or Fragile-X-syndrome.

Both the clinically diagnosed child having ADHD and his non-affected sibling were similarly screened using the standard procedures of the IMAGE project described elsewhere (Brookes et al. 2006; Rommelse et al. 2007). Briefly, screening questionnaires (parent and teacher Conners' long version rating scales (Conners 1996) and parent and teacher strengths and difficulties questionnaires (Goodman 1997)) were used to identify children with ADHD symptoms. The reliability and validity of both questionnaires have been established (Conners 1996; Goodman 1997). T-scores ≥ 63 on the Conners' ADHD-subscales (DSM-IV Inattention, DSM-IV hyperactive-impulsive, and DSM-IV ADHD Total) and scores $>$ 90th percentile on the SDQ-hyperactivity scale were considered as clinical. A semi-structured, standardized, investigator-based interview was administered for the child with ADHD: the parental account of children's symptoms (PACS) (Taylor 1986; Taylor et al. 1991). For details of the standardized algorithm that was applied to derive each of the 18 DSM-IV ADHD symptoms, readers are referred to Rommelse et al. (2007). The Conners' long version for both parents and teachers was completed for control children. Control children had to obtain non-clinical scores on both the parent and teacher version (Conners DSM-IV Total: T-score ≤ 62). Table 1 provides the characteristics of the three groups.

Full-Scale IQ was estimated by four subtests of the WISC-III or WAIS-III (depending on the child's age): Vocabulary, Similarities, block design and picture completion (Wechsler 2000, 2002). These subtests are known to correlate between 0.90 and 0.95 with the Full-Scale IQ (Groth-Marnat 1997). IQ testing took place while the children were off medication.

Table 1. *Sample characteristics*

	Boys with ADHD		Non-affected brothers		Control boys		$F(2,44)$	p	Contrasts
	$n=14$		$n=18$		$n=15$				
	M	SD	M	SD	M	SD			
Age in years	12.0	1.3	11.1	2.7	9.8	1.9	4.0	0.03	1>3
IQ	96.4	12.0	106.4	15.7	108.4	11.2	3.2	0.05	1<3
% Right handed	100.0		94.4		73.3		6.2[1]	0.05	1&2>3
Conners' parent									
DSM-IV: Inattentive	68.6	6.2	45.8	4.8	44.1	4.0	107.6	<0.001	1>2&3
DSM-IV: Hyperactive-impulsive	71.7	8.9	49.8	7.2	46.7	3.8	56.6	<0.001	1>2&3
DSM-IV: Total	71.7	6.9	47.6	5.6	44.7	4.1	102.7	<0.001	1>2&3
Oppositional	65.4	9.2	52.5	12.6	47.3	8.0	12.9	<0.001	1>2&3
Anxious-shy	59.6	12.5	48.4	8.3	51.5	13.2	3.7	0.03	1>2
Conners' teacher									
DSM-IV: Inattentive	65.0	4.5	47.3	4.9	44.1	4.6	83.4	<0.001	1>2&3
DSM-IV: Hyperactive-impulsive	65.6	8.8	48.0	6.0	44.0	2.2	50.1	<0.001	1>2&3
DSM-IV: Total	66.7	6.2	47.6	5.4	43.7	3.6	82.2	<0.001	1>2&3
Oppositional	55.9	9.6	48.7	6.3	46.9	4.2	6.7	0.003	1>2&3
Anxious-shy	60.9	7.9	54.8	9.6	54.0	12.9	2.6	0.09	–

1 Boys with ADHD; *2* non-affected brothers; *3* control boys.
ADHD Attention-deficit/hyperactivity disorder; *DSM-IV* diagnostic and statistical manual for mental disorders (4th edition); [1] χ^2.

Measures

Apparatus

A Pentium IV computer with a processor speed of 2.3 GHz controlled the timing of the events and recorded response times. Displays were presented on an Iiyama 21″ SVGA monitor with a resolution of 1024×768 pixels and an 85-Hz refresh rate. A second computer controlled the registration of saccades on-line. Saccades were registered by means of a video-based eye tracker (SR Research Ltd., Canada). The Eyelink2 system has a 500 Hz temporal resolution and a spatial resolution of 0.04°. The system used an infrared video-based tracking technology to compute the pupil centre and pupil size of both eyes. An infrared head mounting tracking system monitored head motion. In line with standard procedures used in eye-tracking studies (Van der Stigchel et al. in press; Van der Stigchel and Theeuwes 2006), both eyes were monitored, but only data from the left eye were analyzed. An eye movement was considered a saccade either when the movement velocity exceeded 35°/sec or when the movement acceleration exceeded 9500°/sec^2. Although the system compensates for head movements, the participant's head was stabilized using a chin rest. The distance between monitor and chin rest was 65 cm. Participants performed the experiment in a sound-attenuated and dimly lit room.

Memory-guided saccade task

Participants first received verbal instructions accompanied by sketches of the task. They were instructed to fixate the central fixation point (dot), until it disappeared and then to move their eyes to the memorized location. The fixation point (0.4°) was light-gray on a black background. After 1200 msec, a light-gray circle (0.64° in diameter) was presented for 50 msec. This circle was positioned on one of four corner locations of an imaginary square with an angle of 6.8° from the central fixation point. Each target location was equally probable. The circle indicated the location to which a saccade had to be made after a variable delay (the memory location). The delay was either 3000 or 7000 msec, was varied within blocks and was signaled by the removal of the central fixation point. The sequence of trials was counterbalanced and randomized for each participant. Inter trial interval was 2000 msec. The experiment consisted of a training session of 16 trials and an experimental session of 2 blocks of 40 trials.

Task variables to assess visuo-spatial working memory were: (1) the accuracy of saccades toward the memorized location of the target, defined as the percentage of trials in which the participant correctly executed an eye movement to the memory location (i.e., the first saccade had an angular deviation of less than 30° from the centre of the memorized target location) and (2) the latency (in msec) of the correctly performed memory saccades, reflecting the ability to initiate a saccade towards a known, but not visible target. Saccade latency was defined as the interval between fixation offset and the initiation of a saccadic eye movement to the target. If the latency of the saccade was shorter than 80 msec, longer than 1200 msec, or deviating more than 2.5 SDs from the mean latency, the trial was removed from analysis. With respect to the accuracy and latency, only trials were included in which no anticipatory or intrusive saccades were made. Task variables proposed to reflect disinhibition were: (3) percentage of anticipatory saccades (saccades towards the target during the delay period) and (4) percentage of intrusive saccades (saccades directed towards another location than the target during the delay period). Task variables that were not hypothesized as being directly related to visuo-spatial working memory or inhibition, but reflecting more basic processes in the control of saccades, were (5) peak velocity (average speed in degrees/sec), (6) tendency to under- versus overshoot saccades (defined as $100 \times$ [post-saccadic position error/distance from initiation of saccade to target location]) and (7) duration (in msec). These last three variables were measured for the first saccade that was made, in trials in which no anticipatory or intrusive saccades were made, and participants made a correct eye movement to the memorized location.

Procedure

Testing of all children took place at the VU University Amsterdam. All children were off medication for at least 48 h (stimulants, 13 boys with ADHD) or longer (non-stimulants, 1 boy with ADHD) before testing to allow complete washout (Pelham et al. 1999). At the end of the session, a gift worth approximately $5 was given. The study was approved by the medical-ethical committee and an informed consent was obtained from the parents and children of twelve years and older. Each session started with a

nine-point grid calibration procedure. Participants were required to produce saccades towards nine fixation points sequentially appearing at random in a 3×3 grid. In addition, simultaneously fixating the central fixation point and pressing the space bar recalibrated the system by zeroing the offset of the measuring device at the start of each trial.

Statistical analysis

In line with standard procedures, a trial was excluded from analysis when no saccade or a saccade less than 3° occurred (Van der Stigchel and Theeuwes 2006). Alpha was set at 0.05. To test group differences for visuo-spatial working memory, inhibition, and oculomotor control, a linear mixed model was used with group (three groups: boys with ADHD, non-affected brothers and control boys) as fixed factor, delay (three versus seven seconds) as repeated measure, and family as a random effect to account for within family correlation. The interaction between group and delay was implemented in the model, in order to test whether a longer delay would emphasize group differences. Age was implemented as a covariate, since the control group was younger than the ADHD group. Analyses were repeated using IQ as a second covariate, which revealed almost the same results. Therefore, results were presented without IQ as covariate, but results with IQ as covariate were also presented when different from the main analyses.

Results

Visuo-spatial working memory: accuracy and latency

There was a main effect of group on *accuracy* ($F(2,47.1) = 3.14$, $p = 0.05$). Children with ADHD and their non-affected siblings were less accurate than controls ($p = 0.06$ and 0.02) but did not differ from each other ($p = 0.77$). There was a marginally significant main effect of delay ($F(1,47.0) = 3.57$, $p = 0.07$), in which children were overall less accurate when they had to wait seven seconds as opposed to three. There was no significant interaction between group and delay ($F(2,47.0) = 0.20$, $p = 0.82$) (see Fig. 1 left panel).

Groups did not differ with respect to *latency* ($F(2,47.1) = 1.29$, $p = 0.29$). Children with ADHD and their non-affected brothers were equally fast as controls in making a saccade towards the memorized target. Delay had a strong effect on latency ($F(1,47.1) = 44.66$, $p < 0.001$): saccades were faster, when children had to wait seven seconds compared to three seconds. The interaction group by delay was not significant ($F(2,47.1) = 0.64$, $p = 0.53$) (see Fig. 1 right panel).

Disinhibition: anticipatory and intrusive saccades

Groups differed marginally in the *percentage of anticipatory saccades* ($F(2,30.0) = 2.65$, $p = 0.09$), a measure hypothesized to relate to disinhibition (Ross et al. 2000). Children with ADHD made significantly more anticipatory saccades than controls ($p = 0.03$). Non-affected brothers formed an intermediate group, since they did not differ significantly from their brothers with ADHD ($p = 0.32$) nor from controls ($p = 0.12$). This main effect became non-significant when IQ was used as covariate ($F(2,32.4) = 1.92$, $p = 0.16$), because children with a higher IQ had less anticipatory saccades and the control group had a higher IQ than the ADHD group. There was no significant main effect of delay ($F(1,47.0) = 0.40$, $p = 0.53$), nor was there a significant interaction between group and delay ($F(2,47.0) = 1.04$, $p = 0.36$), indicating these group differences to be present regardless of delay manipulation (see Fig. 2 left panel).

Groups differed in the *percentage of intrusive saccades* ($F(2,47.8) = 4.67$, $p = 0.01$). Pairwise comparisons indicated that children with ADHD made more intrusive saccades than their non-affected siblings ($p = 0.006$) and controls ($p = 0.02$). Non-affected siblings did not differ from controls ($p = 0.92$). There was a significant main effect of delay ($F(1,47.0) = 16.13$, $p < 0.001$), suggesting more intrusive saccades were made when children had to wait seven as opposed to three seconds. No significant

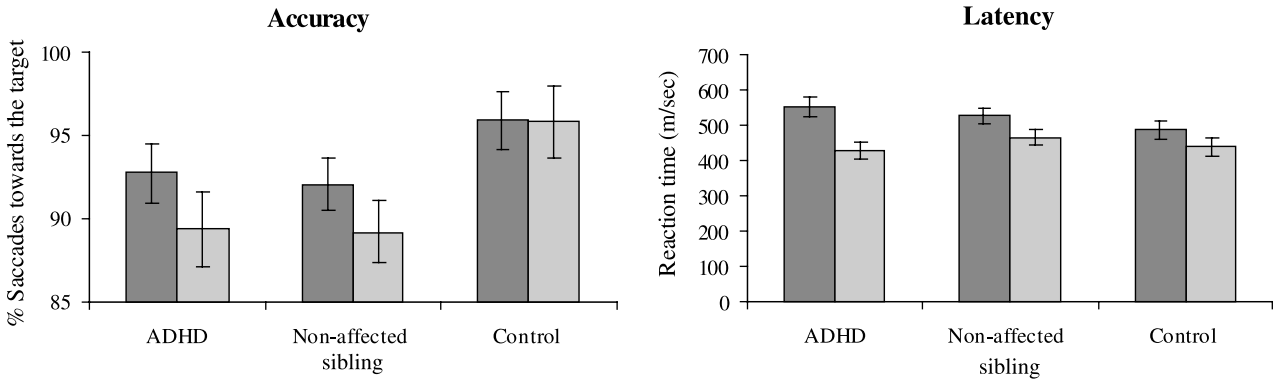

Fig. 1. Visuo-spatial working memory: accuracy and latency of saccades in boys with ADHD, their non-affected brothers and control boys on a memory-guided saccade task. The means are adjusted for the covariate age and error bars represent 1 standard error. ■ 3 Second delay; □ 7 Second delay

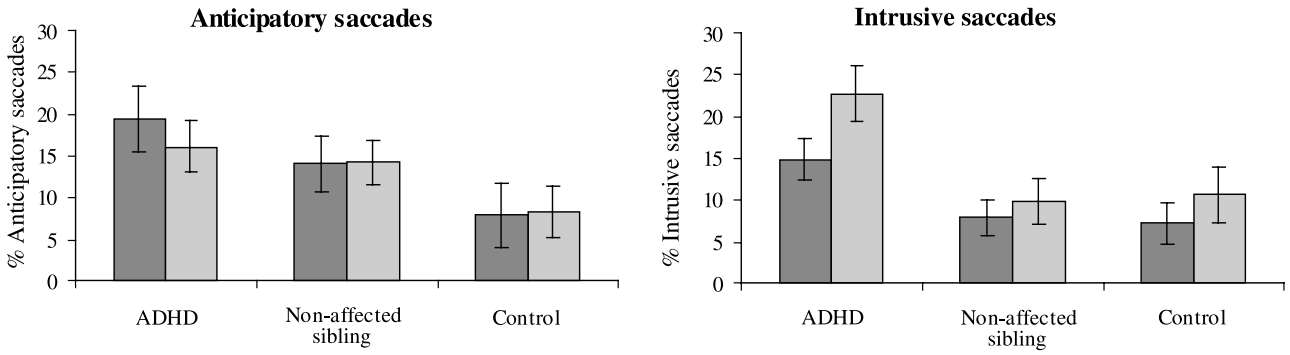

Fig. 2. Disinhibition: percentage of anticipatory and intrusive saccades in boys with ADHD, their non-affected brothers and control boys on a memory-guided saccade task. The means are adjusted for the covariate age and error bars represent 1 standard error

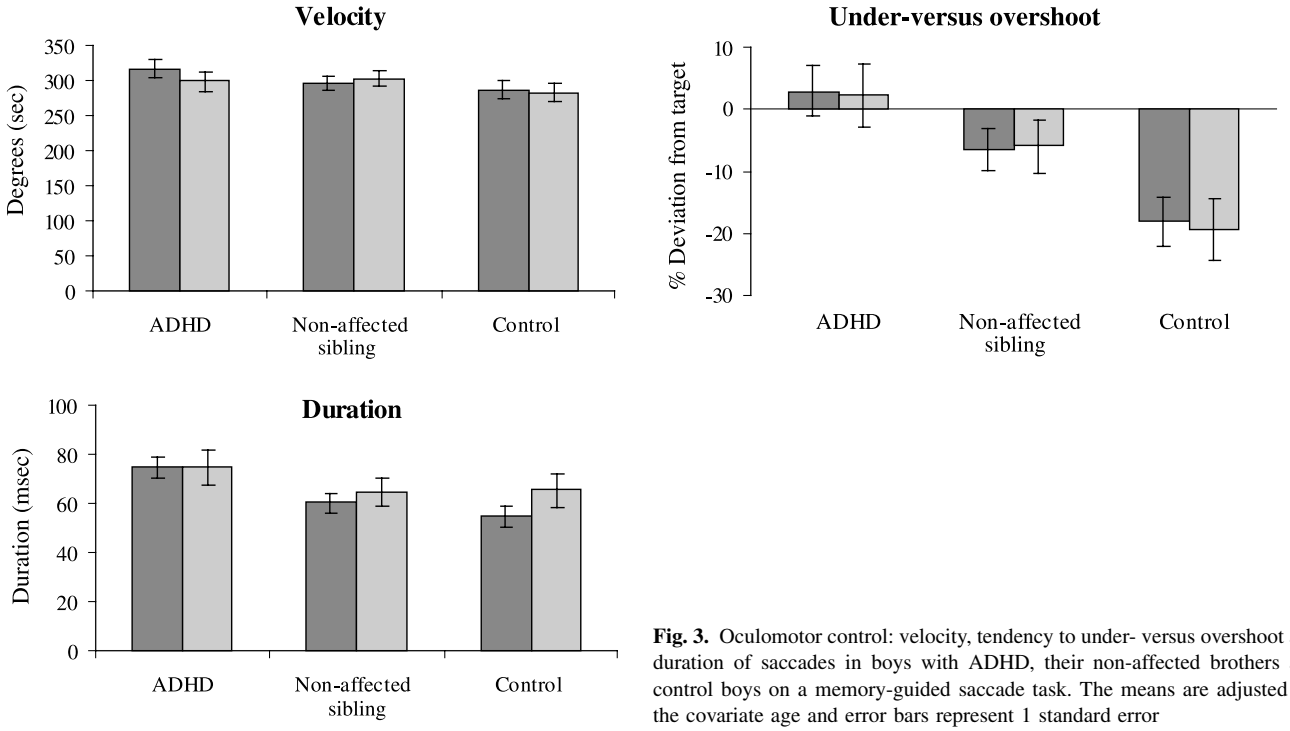

Fig. 3. Oculomotor control: velocity, tendency to under- versus overshoot and duration of saccades in boys with ADHD, their non-affected brothers and control boys on a memory-guided saccade task. The means are adjusted for the covariate age and error bars represent 1 standard error

group by delay interaction was present ($F(2,47.0) = 2.16$, $p = 0.13$), indicating that group differences were not influenced by delay manipulation (see Fig. 2 right panel).

Oculomotor control: velocity, under- versus overshoot, and duration

No significant effect of group was found for *velocity* ($F(2,47.1) = 0.98$, $p = 0.38$). The saccades of children with ADHD and their non-affected brothers were equally fast as those of controls. There was no effect of delay ($F(1,47.0) = 1.43$, $p = 0.24$), nor was the group by delay interaction significant ($F(2,47.0) = 2.31$, $p = 0.11$) (see Fig. 3 left panel).

Groups differed significantly in their tendency to *under-versus overshoot* saccades ($F(2,47.1) = 7.28$, $p = 0.002$). Normal controls tended to undershoot the memorized location but children with ADHD and their non-affected siblings showed this tendency to a lesser degree than controls ($p < 0.001$ and $p = 0.02$, respectively). Children with ADHD marginally significantly differed from their non-affected siblings ($p = 0.09$). The reduced tendency to undershoot even resulted in an overshoot of the memorized target in children with ADHD, though not in the non-affected siblings. This is illustrated with example saccades in Fig. 4. Results were not influenced by delay manipulation ($F(1,47.0) = 0.10$, $p = 0.75$) or an interaction between group and delay ($F(2,47.0) = 0.61$, $p = 0.55$) (see Fig. 3 middle panel).

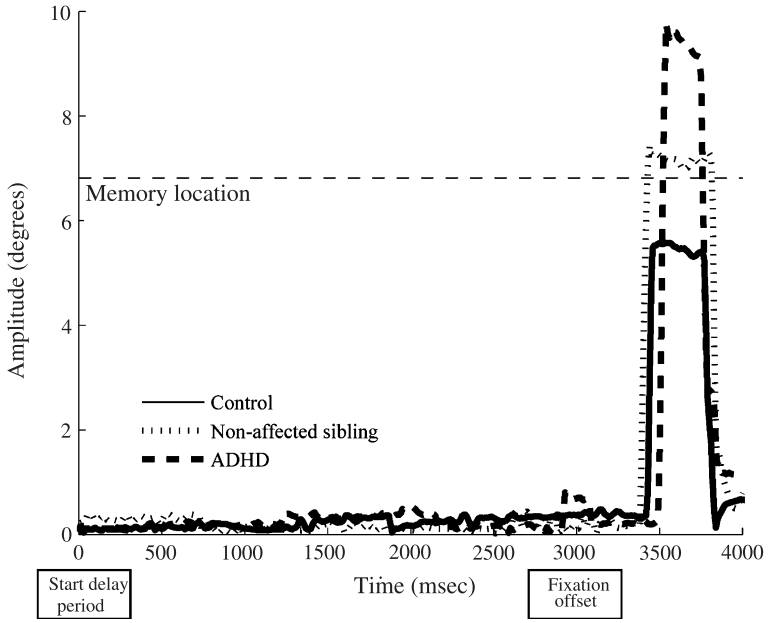

Fig. 4. Example saccades of a boy with ADHD, a non-affected brother and a control boy on a 3-second delay trial of the memory-guided saccade task illustrating group differences for the tendency to under- versus overshoot the memorized target location

Since velocity was comparable across groups, but groups differed with respect to the length of the trajectory of saccades, consequently groups differed marginally in *duration* ($F(2,40.9) = 2.79$, $p = 0.07$). The saccades of children with ADHD were of longer duration than those of their non-affected siblings and controls ($p = 0.06$ and 0.04, respectively). Non-affected siblings did not differ from controls ($p = 0.66$). A significant effect of delay was present ($F(1,47.0) = 5.93$, $p = 0.02$), suggesting the duration of a saccade was longer in the seven-second delay compared to the three-second delay. No significant interaction between group and delay was present ($F(2,47.0) = 1.29$, $p = 0.28$) (see Fig. 3 bottom panel).

Discussion

This study examined the performance of boys with ADHD, their non-affected brothers and control boys on a memory-guided saccade task. By including children with ADHD as well as their familially-at-risk siblings, we could investigate whether deficits on the memory-guided saccade task related to a familial risk for ADHD. We tested whether boys with ADHD and possibly their non-affected brothers deviated from controls on measures of visuo-spatial working memory, inhibition and oculomotor control. It was hypothesized that group differences would be larger when a seven-second delay was applied compared to a three-second delay, because a seven-second delay was predicted to be more taxing for working memory and inhibitory control compared to a three-second delay.

Visuo-spatial working memory

We found boys with ADHD to be less accurate in their saccades towards the memorized target, which is in line with another study reporting on girls with ADHD using a memory-guided saccade task (Castellanos et al. 2000) but inconsistent with others (Ross et al. 1994a, 2000; Mostofsky et al. 2001), who reported no impairments in accuracy towards memorized targets in ADHD. The inconsistent results for accuracy in studies using memory-guided saccade tasks is worrisome, the more so since meta-analyses suggest effect sizes for ADHD versus controls in standard cognitive measures of visuo-spatial working memory are fairly robust (Martinussen et al. 2005). This might relate to differences in paradigms used (for example, a large variability in delay periods used in various studies, ranging from 0.8 till 7 seconds) and/or relate to differences in demographics in participants (only males, only females, males and females; children or adults). Nevertheless, our study contributes further to the existent findings by showing that also non-affected siblings have a reduced accuracy towards the memorized target, which suggest impairments in the accuracy of visuo-spatial working memory may form a familial deficit (i.e., endophenotype) in ADHD.

We did not find group differences for latency, which is consistent with most (Ross et al. 1994a, 2000; Castellanos et al. 2000), but not all studies (Mostofsky et al. 2001). Since no group differences were found in latency in our study and the majority of other studies, this suggests that the overall visual processing and visual motor programming appear unimpaired in children with ADHD and sib-

lings (Leigh and Kennard 2004)[1]. This is also consistent with findings in visual search tasks of ADHD children and controls (Sergeant and Scholten 1985).

Disinhibition

Children with ADHD portrayed a higher percentage of anticipatory and intrusive saccades than controls, which is consistent with studies using memory-guided paradigms and other eye tracking paradigms in patients with ADHD (Ross et al. 1994a, 2000; Castellanos et al. 2000; Mostofsky et al. 2001). These anticipatory and intrusive saccades are present irrespective of the paradigm used to study saccades and are also present in adults with ADHD (Munoz et al. 2003; Feifel et al. 2004), despite an age dependent decline in anticipatory and intrusive saccades (Ross et al. 1994b). This may suggest that these abnormal saccades form an important, characteristic sign of pathology in ADHD. It has been hypothesized that these unwanted saccades are mediated by abnormalities in a prefrontal cortex – basal ganglia network (Feifel et al. 2004), dorsolateral prefrontal cortex and frontal eye fields (Cairney et al. 2001), structures which are also implicated in ADHD (Durston et al. 2003). Our study adds important knowledge with respect to these anticipatory and intrusive saccades: non-affected siblings exhibited an intermediate level of anticipatory saccades in between their affected siblings and controls. This suggests that anticipatory saccades may be related to a familial risk for ADHD and may form a putative endophenotype of ADHD (Durston et al. 2004). In contrast, intrusive saccades were only present in the affected, but not in non-affected children, suggesting these deficits may have been caused by the presence of ADHD itself or relate to some unique risk factors for ADHD that are not shared between the affected and non-affected siblings (Durston et al. 2004).

Oculomotor control

An intriguing finding is the alteration in oculomotor control in both children with ADHD and their non-affected siblings. Normal controls tended to undershoot the memorized location, which has been previously reported in healthy participants (Becker and Fuchs 1969; Henson 1979; Leigh and Kennard 2004). Children with ADHD and their non-affected siblings showed this tendency to a lesser degree which resulted in an overshoot of the memorized target in affected children. This resulted in a smaller deviation from the memorized target in children with ADHD and non-affected siblings compared to controls, which may suggest that children with ADHD and their non-affected siblings were objectively speaking more accurate than controls in directing their saccades. However, because the tendency to undershoot in healthy controls is used as baseline, a tendency to overshoot is present both in children with ADHD and siblings, which may be familial and a putative endophenotype. Since the saccades of children with ADHD had a substantially longer trajectory than those of controls but there were no group differences for velocity, the total duration of saccades was longer in ADHD boys than in controls, a finding consistent with a previous study (Munoz et al. 2003).

There might be several explanations for the altered oculomotor control in children with ADHD and their non-affected siblings. First, the altered oculomotor control might be explained by problems in saccadic metria possibly caused by abnormalities in the cerebellum (Robinson et al. 1993; Leigh and Zee 1999; Leigh and Kennard 2004). Reduced cerebellar volumes throughout the development have been documented in patients with ADHD (Castellanos et al. 2002). The Purkinje cells in the dorsal vermis of the cerebellum encode the time, required to align the saccade with the target (Their et al. 2002). Since there is no time for visual feedback during a saccade, control depends on internal monitoring of neural signals (Leigh and Kennard 2004). The finding of overshooting saccades in children with ADHD and their siblings compared to controls may imply that the internal monitoring of neural signals is different in children with ADHD and their siblings compared to normal children. Since the cerebellum is involved both in visually-guided saccades as well as memory-guided saccades (Nitschke et al. 2004), one would expect to find oculomotor abnormalities in children with ADHD regardless of the paradigm used. However, no such abnormalities have been reported in previous studies using prosaccade tasks, in which subjects were simply asked to produce a saccade towards a visible target. The second

[1] Previous studies have shown that children with ADHD can be more variable in their reaction times/latencies even in the absence of group differences for mean reaction times (Klein et al. 2006). Therefore, we reran our analyses on the variability of latencies. We found that groups differed with respect to the variability in their saccade latencies (F (2,16.0) = 4.04, $p = 0.04$). Children with ADHD were more variable in their saccade latencies than controls ($p = 0.009$). Non-affected siblings formed an intermediate group, marginally differing from the ADHD group or the control group (both $p = 0.09$). Furthermore, delay had a significant effect ($F(1,47.0) = 26.18$, $p < 0.001$), with less variability in latency when the delay was seven seconds compared to three. No group by delay interaction was present ($F(2,47.0) = 1.15$, $p = 0.33$). Our results indicate this variability to be present in a paradigm without requiring a manual response (i.e., oculomotor paradigm) and possibly to be familial, since non-affected siblings exhibited an intermediate level of variability in saccade latency in between their affected siblings and controls.

explanation for the altered oculomotor control in ADHD and non-affected siblings may, therefore, lie in the nature of memory-guided saccades. That is, a saccade towards an invisible (memorized) target may be of a different nature than a saccade towards a visible target. Evidence for this was reported by Sawaguchi and Goldman-Rakic (1994) who reported dopamine antagonists had an effect on the accuracy and latency of memory-guided saccades but not on the accuracy and latency of sensory-guided saccades. It may thus be that the altered oculomotor control in children with ADHD and their non-affected siblings is restricted to memory-guided saccades only, possibly related to alterations in the dopaminergic systems found in ADHD (Levy 1991; Levy and Swanson 2001). We do not believe dimly illumination during testing explains group differences in under- versus overshooting the memorized target. Even though Gnadt and colleagues (1991) reported memory-guided saccades to be less accurate in the dark than in the light, Bakola and colleagues (2007) reported brain regions involved in memory-guided saccades overlapped extensively when performed in the light and the dark. Furthermore, some illumination was present during testing allowing the visual contours of the experimental room to be exposed and illumination during testing was identical for all children, making it unlikely illumination explains group differences in under- versus overshooting memory-guided saccades.

Effect of delay manipulation

As expected, we found a significant effect of delay on the measures of visuo-spatial working memory (accuracy and latency) and on a measure of disinhibition (percentage of intrusive saccades). Children were less accurate and made more intrusive saccades, when they had to wait seven seconds as opposed to three seconds. These findings supported the hypothesis that longer delay periods put heavier loads on working memory and inhibitory processes (Sawaguchi and Goldman-Rakic 1994; Ozonoff and Stayer 2001). The effect of delay was reversed, however, for latency: children were faster (and less variable), when they had to wait seven as opposed to three seconds. The latter finding is generally explained by increased response preparation in the longer delay (Niemi and Näätänen 1981). The measures of oculomotor control were not influenced by delay manipulation, except for the duration of a saccade. With delay time being at three and seven seconds, these parameters were set at the very low and top end compared to the existing literature. The finding that delay time does not affect velocity or tendency to under- or overshoot suggests that the processes underlying oculomotor functioning are similar across delay durations.

In addition, no significant group by delay interaction was found for any of the variables studied. This suggests that, in contrast to predictions, group differences were not larger in the seven-second delay compared to the three-second delay. This finding is consistent with the findings reported by Ross et al. (2000), in which differences between adults with ADHD and normal adults were unrelated to the delay manipulation used (one versus three seconds). The absence of a group by delay interaction for all measures might indicate that visuo-spatial working memory and inhibition are unimpaired in children with ADHD and their non-affected siblings, but alternatively probably relates to the relative simplicity of the task, reflected by a ceiling effect in accuracy on both delay durations, and possibly relates to a lack of power due to small sample sizes.

Limitations

This study suffered from some limitations. First, groups differed with respect to IQ. Even though results with and without covarying for IQ revealed comparable results except for percentage of anticipatory saccades, it can not be ruled out conclusively that group differences on IQ have influenced the results. Future research using groups matched for IQ could clarify whether results are indeed robust and not carried by IQ effects. Second, sample sizes were relatively small, which might have resulted in undetected effects because of lack of power. However, even though sample sizes were small, group effects were significant, underlining the importance of group differences. Third, additional measures of working memory and inhibition would have considerably strengthened the study, since these measures would have allowed analyses on the convergent and divergent validity of the measures of the memory-saccade task. Fourth, no girls were tested because we wanted to minimize the differences between groups concerning factors other than diagnosis, though this limits the generalization of our findings to girls with ADHD and their non-affected sisters. It appears, though, that similar deficits in visuo-spatial working memory, inhibition and oculomotor control might be expected in girls with ADHD, since comparable brain abnormalities (Castellanos et al. 2001), comparable patterns of familial transmission (Faraone et al. 2000) and comparable deficits on a memory-guided saccade task (Castellanos et al. 2000) have been observed in girls with ADHD compared to boys with ADHD. Furthermore, even though it has been observed that girls may suffer less from executive deficits than boys (Seidman

et al. 1997) which might also translate in less severe deficits on a memory-guided saccade task, gender differences for executive deficits are not a consistent finding (Seidman et al. 2005). Future research is needed to examine possible deficits on a memory-guided saccade task in girls with ADHD and their non-affected sisters.

Conclusion

We have found evidence for diminished accuracy of visuospatial working memory and elevated numbers of anticipatory saccades in boys with ADHD as well as their non-affected brothers using a memory-guided saccade task. Elevated numbers of intrusive saccades were only found in children with ADHD, but not in their non-affected brothers, suggesting these types of saccades not to be related to a familial predisposition for ADHD. Interestingly, deficits were found in oculomotor control: unlike controls, who undershoot the memorized target, children with ADHD and their non-affected siblings showed a reduced tendency to undershoot the memorized location. This might be related to alterations in the functioning of the cerebellum or, alternatively, related to alterations in the dopaminergic transmission which would only affect memory-guided saccades and not sensory-guided saccades. The finding that observed deficits are not only present in children having ADHD, but also in their non-affected siblings, may suggest these problems are related to a familial risk for ADHD and form putative endophenotypes for the disorder.

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